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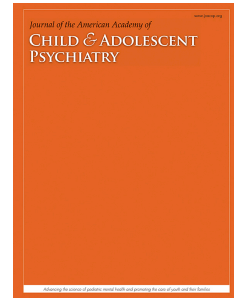
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Evidence From Two Representative Twin Samples

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Is There a Female Protective Effect Against Attention-Deficit/Hyperactivity Disorder?
Evidence From Two Representative Twin Samples

RH: Female Protective Effect Against ADHD

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ABSTRACT

Objective: Attention-deficit/hyperactivity disorder (ADHD) is more frequent in males than females. The “female protective effect” posits that females undergo greater exposure to etiological factors than males in order to develop ADHD, leading to the prediction that relatives of females with ADHD will display more ADHD behaviors. We thus tested whether co-twins of females displaying extreme ADHD traits would display more ADHD traits than co-twins of males displaying extreme ADHD traits.

Method: Parents of approximately 7,000 pairs of non-identical twins in Sweden, and around 4,000 pairs of twins in England and Wales, completed dimensional assessments of ADHD traits. Probands were selected on the basis of scoring within the highest 10% of the distribution in each sample. Dimensional scores of co-twins of probands, as well as the categorical recurrence rate, were investigated by proband sex.

Results: Co-twins of female probands displayed higher mean ADHD trait scores (\bar{x} =0.62-0.79) than co-twins of male probands (\bar{x} =0.38-0.55) in both samples. This trend was significant in the Swedish sample ($p<.01$) and when the two samples were merged into a single, larger sample ($p<.001$). When the samples were merged, there was also a significant association between proband sex and co-twin’s categorical status, with more co-twins of female probands also being probands than co-twins of male probands.

Conclusion: These findings support a female protective effect against ADHD behaviors, suggesting that females require greater exposure to genetic and environmental factors associated with ADHD in order to develop the condition.

Key words: ADHD, sex differences, genetics, twin study

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition characterized either by excessive hyperactivity and impulsivity, inattentiveness, or a

combination of these symptoms¹. Epidemiological studies suggest that, overall, ADHD affects between 5-7% of the population². Notably, ADHD appears to be substantially more common in males than females. A study of ten European countries, for instance, indicated that males with ADHD outnumbered females with ADHD by ratios of two to one to sixteen to one³. The excess of males with ADHD has been further confirmed by meta-analyses, with four times as many males than females thought to be affected^{2,4}.

A number of twin studies have established that ADHD is among the most heritable of neuropsychiatric conditions⁵⁻⁹. The high heritability of ADHD does not vary markedly whether it is conceptualized as a categorical, diagnosed condition⁵⁻⁶ or treated as a continuous trait in the general population⁷⁻⁹, thus indicating that severe forms of ADHD may be linked genetically with milder, subclinical traits of ADHD in the general population. Such studies, however, have yet to shed light on the reasons why ADHD appears to be so much more common in males than females.

One possible explanation for the sharp sex discrepancy in ADHD prevalence is a putative “female protective effect” model. Under this model, females would be predicted to require greater exposure to genetic and environmental factors associated with ADHD than males in order to display sufficient ADHD behaviors to warrant a diagnosis, thus meaning that fewer females would be expected to be diagnosed with ADHD than males¹⁰⁻¹¹. As such, one would expect more causal factors to be present in the families of females with ADHD, leading to the prediction that ADHD and ADHD behaviors will be more prevalent in the relatives of females with ADHD. The female protective effect is presently receiving considerable attention in relation to autism spectrum disorders (ASD), which are similarly male-biased conditions. In one study, for example, the fraternal co-twins of females displaying a high degree of autistic traits displayed more autistic traits than did co-twins of

males with high degrees of autistic traits, and were also more likely to display high scores themselves¹².

Very few studies have tested for the existence of a female protective effect against ADHD. A recent Swedish investigation suggested that merely having a female co-twin is associated with displaying a greater degree of ADHD traits than having a male co-twin, although this study did not take account of the degree to which the index twin displayed ADHD symptoms¹³. In one study of a US-based twin sample, traits of ADHD were examined in the co-twins of individuals displaying a high degree of traits of ADHD. Co-twins of females displaying extreme ADHD traits displayed significantly greater ADHD-like behaviors than the co-twins of males displaying extreme traits of ADHD¹⁴. Of note, however, the effect was not present for the co-twins of the most severely affected twins, perhaps owing to the small effect size and lower number of twins displaying the very highest scores.

As a consequence, we aimed to test for the existence of a female protective effect against ADHD behaviors in two independent, large-scale European twin samples. We first tested whether the co-twins of females displaying extreme degrees of ADHD traits would exhibit more continuous ADHD traits than the co-twins of high-scoring males. Second, we sought to test whether high-scoring female twins were more likely to have a high-scoring co-twin than high-scoring male twins. The one previous study documenting this effect reported that the effect size was small¹⁴; thus, we not only aimed to test for the female protective effect against ADHD in our two samples independently, but also pooled the two samples to increase power. We expected, in light of existing evidence, to find evidence of a female protective effect against ADHD behaviors¹³⁻¹⁴.

METHOD

Participants

Data were collected from participants in two representative, community-based twin studies. The Child and Adolescent Twin Study in Sweden (CATSS) is a study of twins born in Sweden since 1992. Initially, the twins were contacted in connection with their ninth birthdays¹⁵. For the present study, data were collected from twins participating in CATSS when they were aged 9. The second sample comprised participants in the Twins Early Development Study (TEDS); TEDS is a sample of twins born in England and Wales between 1994 and 1996¹⁶. Data for the present study were collected from TEDS participants when twins were aged 8 years. TEDS and CATSS are representative of the populations of England and Wales, and Sweden, respectively¹⁵⁻¹⁶.

Both CATSS and TEDS comprise both monozygotic (MZ) and dizygotic (DZ) twins, although only DZ twins were included in this study owing to the fact that the genetic resemblance of two DZ twins within a pair is the same as the resemblance between two singleton siblings (approximately 50% of their segregating DNA code on average). Both same-sex and opposite-sex DZ twins were included. In CATSS, families of 6,817 pairs of DZ twins returned data, while 4,309 participating families in TEDS returned data. In CATSS, exclusions were conducted for known brain injuries and chromosomal syndromes (n=113), leaving 6,704 DZ twin pairs. Participants in TEDS were excluded for genetic and chromosomal syndromes, extreme perinatal complications, and missing first contact data (n=254), leaving 4,055 pairs of DZ twins. Combined, there were 10,759 DZ twin pairs across the two samples.

CATSS has ethical approval from the Karolinska Institutet Ethical Review Board, while TEDS has ethical approval from the King's College London, Institute of Psychiatry, Psychology and Neuroscience Ethics Committee.

Measures

In CATSS, the ADHD modules of the Autism-Tics, ADHD, and Other Comorbidities inventory (A-TAC)¹⁷ were administered to parents of the twins over the telephone. There are two ADHD modules, assessing hyperactivity/impulsivity and inattentiveness, comprising a total of 19 items that correspond closely to *DSM-IV* criteria for ADHD¹. Each item comprised a question, answered “yes” (for a score of 1), “yes, to some extent” (for a score of 0.5), or “no” (for a score of 0). Thus, the maximum possible score was 18. In the sample of DZ twins used in the present study, the A-TAC ADHD module had strong internal consistency ($\alpha = .92$). A prior study reported strong construct validity for the scale, with 92% sensitivity and 75% specificity for detecting ADHD¹⁸. The A-TAC also comprises two subscales, assessing ADHD subtypes: Hyperactivity/Impulsivity (10 items) and Inattention (9 items).

Parents of twins participating in TEDS completed the ADHD subscale of the Conners’ Parent Rating Scale–Revised (Conners ADHD)¹⁹. The measure was mailed out to parents of the twins, who completed and returned it. Like the A-TAC, the Conners ADHD measure comprises 18 items that are closely linked with the *DSM-IV* criteria for ADHD¹. Each item comprised a statement in response to which the parents rated, on a 0-3 scale, the extent to which each item was true of their children. The maximum possible score was 54. In the present study, the Conners ADHD showed strong internal consistency ($\alpha = .91$). Previously, individuals with ADHD have been shown to score more highly on the measure than controls¹⁹, supporting its construct validity. As with the A-TAC, Conners ADHD comprises Hyperactivity/Impulsivity and Inattention subscales (9 items each).

Data Analysis

Proband Selection

In both samples, one twin was randomly selected as the “index twin.” All other twins were co-twins. Probands were selected as the index twins scoring within the highest 10% of the A-TAC and Conners ADHD distributions, with such a cut-off designed to maximize

statistical power while capturing severe-enough cases. Thus, probands in CATSS were selected on the basis of A-TAC scores of 6.5 or more, while TEDS probands were defined as index twins scoring at least 23 on the Conners ADHD. Subsequently, analyses were repeated using more conservative cut-offs of 9.5 on the A-TAC and 28 on the Conners ADHD. These cut-offs were designed to capture the highest scoring 5% of each sample, thus testing for a female protective effect in relation to even more extreme scores. Due to the lack of sex-specific diagnostic criteria for ADHD, the same cut-offs were used to select probands, regardless of sex. The number of probands, split by sex, is given in Table 1.

Statistical Analysis

To test whether co-twins of female probands would display higher ADHD trait scores than co-twins of male probands, 3x2 between-subjects analysis of variance (ANOVA) was employed. Proband status of the index twin (male proband, female proband, or control) was the grouping variable, with co-twins' ADHD trait scores acting as the outcome variable. An omnibus test initially compared scores across co-twins of male probands, female probands, and controls, before planned comparisons compared the scores of co-twins of male and female probands. Individual p-values were adjusted for multiple comparisons within each sample using the Bonferroni correction. All reported p-values are adjusted in this manner. Effect sizes were summarized using Cohen's *d*. Effect sizes were interpreted using Cohen's criteria²⁰, with *d* of .20-.49 considered a small effect, .50-.79 medium, and greater than .80 large.

To test whether sex of the probands was associated with whether or not their co-twin would also be a proband, categorical analyses were employed. Using the above identified cut-offs, co-twins were classified as either "affected" (i.e., scoring above a given cut-off) or "unaffected" (i.e., scoring below a given cut-off). Chi-square tests of association were then

used to test whether co-twin status was significantly associated with proband sex. Effect sizes were summarized using odds ratios (ORs).

Analyses were first conducted separately in CATSS and TEDS. To bolster statistical power, a third set of analyses was performed on the two samples combined. The Conners ADHD and A-TAC were both heavily, positively skewed and were therefore log transformed prior to analysis (see Table 2). All co-twin scores used in analyses were standardized by sex of the co-twin, thus ensuring that co-twin sex was controlled for and allowing easier comparability of findings across samples. All analyses were performed in R²¹.

Post hoc analyses subsequently tested for a female protective effect against specific ADHD behaviors. All of the analyses detailed above were repeated on the Hyperactivity/Impulsivity and Inattention subscales of the A-TAC and Conners ADHD. Since these analyses were post hoc, p-values were not adjusted for multiple comparisons.

RESULTS

Descriptive statistics for the A-TAC and Conners ADHD are given in Table 2.

Analysis of Continuous Scores

Mean standardized scores of co-twins of male probands, female probands, and controls are all shown in Figure 1 for the analyses using the 10% cut-offs. In CATSS, scores differed significantly across the three groups ($F_{2,6688}=79.35$, $p<.01$), with co-twins of female probands scoring highest ($\bar{x}=0.62$), followed by co-twins of male probands ($\bar{x}=0.38$), and co-twins of controls ($\bar{x}=-0.05$). Specifically, co-twins of female probands displayed significantly higher A-TAC scores than co-twins of male probands ($t_{6688}=-2.84$, $p<.01$), with a modest effect size of $d=.07$.

Similarly in TEDS, Conners ADHD scores differed significantly across co-twins of male probands ($\bar{x}=0.55$), co-twins of female probands ($\bar{x}=0.79$), and co-twins of controls ($\bar{x}=-0.07$), $F_{2,4040}=102.30$, $p<.001$. Planned contrasts, however, indicated that mean Conners

ADHD scores were not significantly elevated in co-twins of female probands relative to co-twins of male probands ($t_{4040}=-2.36$, $p=.08$, $d=.07$), despite a trend in this direction.

Merging the two samples produced the same pattern; mean ADHD trait scores differed significantly in the three groups ($F_{2,10731}=175.90$, $p<.001$), with co-twins of female probands showing the highest ADHD trait scores ($\bar{x}=0.69$), followed by co-twins of male probands ($\bar{x}=0.45$), and controls ($\bar{x}=-0.06$). The planned contrast confirmed that mean ADHD trait scores were significantly higher for co-twins of female probands than co-twins of male probands ($t_{10731}=-3.73$, $p<.001$, $d=.07$).

All mean ADHD trait scores for co-twins of probands selected under the more severe, 5% cut-offs are given in Table 3. Merging the two samples produced the same pattern of results as the 10% cut-off. Index twin status exerted a significant main effect on the mean ADHD trait scores of co-twins ($F_{2,10731}=95.90$, $p<.001$), with co-twins of female probands displaying the highest ADHD trait scores ($\bar{x}=0.73$), followed by co-twins of male probands ($\bar{x}=0.51$) and controls ($\bar{x}=-0.03$). Mean ADHD trait scores were significantly elevated in co-twins of female probands compared with co-twins of male probands ($t_{10731}=-2.38$, $p<.05$, $d=.05$).

Using a 5% cut-off, the same pattern emerged in each individual sample. In CATSS, mean A-TAC scores differed significantly across co-twins of male probands ($\bar{x}=0.43$), female probands ($\bar{x}=0.69$), and controls ($\bar{x}=-0.03$), $F_{2,6688}=46.39$, $p<.01$; however, mean A-TAC scores for co-twins of female probands were not significantly higher than mean A-TAC scores for co-twins of male probands ($t_{6688}=-2.10$, $p=.16$, $d=.05$). The same result emerged for TEDS. While the main effect of index twin status was significant ($F_{2,4040}=51.63$, $p<.001$), with co-twins of female probands showing the highest mean Conners ADHD scores ($\bar{x}=0.79$), followed by co-twins of male probands ($\bar{x}=0.62$) and controls ($\bar{x}=-0.04$), mean

Conners ADHD scores for co-twins of female probands were not significantly higher than mean scores for co-twins of male probands ($t_{4040}=-1.10$, $p=.27$, $d=.03$).

Analysis of Categorical Recurrence

Table 4 shows the number of affected and unaffected co-twins by proband sex for each sample and cut-off. Using a 10% cut-off to select probands, the association between proband sex and co-twin status was only significant when CATSS and TEDS were merged ($\chi^2_1=5.21$, $p<.05$, $OR=0.70$ [0.52/0.94]), with a greater proportion of co-twins of female probands (29%) than co-twins of male probands (22%) showing higher ADHD trait scores.

In CATSS, a greater proportion of co-twins of female probands scoring above the 10% also scored above the cut-off (15% of co-twins of female probands compared with 9% of co-twins of male probands). The association was small and non-significant, however ($\chi^2_1=4.67$, $p=.06$, $OR=0.57$ [0.34/0.92]). Similarly in TEDS, 38% of co-twins of female probands scored above the 10% cut-off compared with 29% of co-twins of male probands, although this association was again small and failed to reach significance ($\chi^2_1=3.23$, $p=.14$, $OR=0.66$ [0.43/1.01]).

The findings followed the same pattern when a cut-off that selected 5% of index twins as probands was used. When CATSS and TEDS were merged, there was a significant association between proband sex and co-twin status ($\chi^2_1=6.38$, $p<-.05$, $OR=0.54$ [0.35/0.86]), with a greater proportion of co-twins of female probands (26%) than co-twins of male probands (16%) showing a pronounced degree of ADHD traits. In CATSS alone, more co-twins of female probands (21%) than co-twins of male probands (12%) were affected, yet this association was not significant ($\chi^2_1=3.35$, $p=.14$, $OR=0.53$ [0.28/0.99]). The same was true of TEDS: more co-twins of female probands (33%) than co-twins of male probands (22%) were affected, yet this seeming association was not significant ($\chi^2_1=2.46$, $p=.24$, $OR=0.56$ [0.29/1.08]).

Subscale Analyses

Figures 1b and 1c show the mean scores of co-twins of probands on the A-TAC and Conners ADHD subscales (Hyperactivity/Impulsivity and Inattention), with probands scoring within the highest 10% of the subscales. In CATSS, TEDS, and the combined cohorts, co-twins of female probands displayed the highest mean Hyperactivity/Impulsivity scores, followed by co-twins of male probands and co-twins of controls. In all analyses, the mean scores of co-twins of female probands were significantly higher than those of the other two groups ($p < .05$).

Inattention followed the same pattern, as shown in Figure 1c. Co-twins of female probands displayed the highest mean Inattention score, followed by co-twins of male probands and co-twins of controls. The mean scores of co-twins of female probands were significantly higher than both other groups of co-twins in all three analyses ($p < .05$).

These results are shown in full in tables S1-S4, available online.

DISCUSSION

This investigation sought to test whether a female protective effect can account for the substantially elevated prevalence of ADHD in males relative to females²⁻⁴. The results of this study lend partial credence to a female protective effect hypothesis for ADHD. In line with the results of an existing US study¹⁴ and our hypotheses, there was some evidence to indicate that the co-twins of females displaying an extreme degree of characteristic ADHD behaviors displayed more such behaviors themselves than did the co-twins of males showing an extreme degree of ADHD traits. Further, co-twins of females with particularly high ADHD trait scores were more likely to display an extreme degree of ADHD behaviors than were the co-twins of males. As such, these findings tentatively indicate that a female protective effect could be a potentially viable model to aid understanding the development of ADHD.

Our findings provide a platform for future research into the genetic basis of ADHD to build upon. While twin studies of ADHD have consistently supported its high heritability⁵⁻⁹, elucidating the precise genetic mechanisms underpinning ADHD has proven elusive²². The female protective effect model provides an opportunity to raise further research questions in such research. For example, genes can be divided into high-impact and low-impact sets²³. One possibility is that females with ADHD are more likely to inherit higher impact genes associated with ADHD, which are rarer. To illustrate, ASD also more commonly affects males than females²⁴, and recent twin and family studies support a female protective effect against ASD^{12,25}. A genetic study then indicated that females with ASD displayed a higher degree of larger copy number variants, which were more likely to be maternally inherited¹¹. Similar studies of ADHD may well prove useful in furthering our understanding of the etiology of ADHD.

Indeed, while our study did not investigate any specific etiological mechanisms associated with ADHD, our findings suggest that investigating the degree of exposure to etiological factors associated with ADHD in males and females with the condition may be a worthwhile future research direction. While the above example mentioned larger, rarer copy number variants, one might also test whether females with ADHD exhibit a greater number of smaller, common genetic variants. Indeed, in using polygenic scores, which have yielded useful insights in the genetic architecture of ADHD²⁶, one could investigate whether females with ADHD display a greater degree of common genetic variants associated with ADHD than males with ADHD²⁷.

One could also extend this to causal environmental factors. While twin studies indicate that genetic factors seem to outweigh environmental factors in the etiology of ADHD⁵⁻⁹, research has implicated certain environmental exposures with ADHD. For instance, lower birth weight is thought to be a causal environmental factor in ADHD²⁸⁻²⁹. It

may be that females with ADHD undergo greater exposure to such factors compared with males; for instance, could females with ADHD display an even lower birth weight than males with ADHD?

The presence of a female protective effect against ADHD behaviors also has implications for clinical practice. If clinicians take account of family history when diagnosing ADHD, it may be beneficial to also account for the sex of any previously affected relatives, under the assumption that relatives of females with ADHD are more likely to exhibit ADHD symptoms than relatives of males with ADHD. The caveat to this assertion, however, is that our findings are based only on twin data. The female protective effect against ADHD needs to be replicated in alternative, non-twin samples before such a conclusion can be decisively drawn. For instance, a recent study of ASD found that siblings of female non-twins with ASD were more likely to have ASD than siblings of male non-twins²⁵. Such studies of non-twin relatives are now needed in relation to ADHD.

It does need to be noted that the overall sizes of the effects reported here, where significant, were weak. The effect reported in this paper is less than half the size of the female protective effect in relation to autism reported in a similar study¹². Indeed, significant findings only emerged for the more severe cut-off of 5% when the two samples used were merged to create a larger sample. The small effect size seen here is consistent with that reported previously¹⁴, and so it is quite clear that subsequent studies testing the female protective effect model of ADHD are going to need to depend on large samples.

The small female protective effect seen here does, nevertheless, stress the need not to discount alternative explanations for the increased number of males with ADHD relative to females. There is very limited research considering phenotypic differences between males and females with ADHD. For instance, one study investigated sex differences in ADHD across ten European countries, and reported that females with ADHD displayed more

emotional difficulties³. Furthermore, the *DSM-IV* criteria for ADHD, upon which our measures were based, are based exclusively on observations of males^{1, 30-31}.

Two further possibilities cannot be discounted from our study. While our findings lend support to the notion of a female protective effect against ADHD, it is not mutually exclusive to the hypothesis that males have more risk factors for ADHD. It is also in theory possible that rater contrast effects drove the higher scores seen in co-twins of female probands. Rater contrast effects refer to the scenario whereby parent ratings of one twin are influenced by how they view their co-twin³². To create the observed pattern of results, parents would need to have shown a stronger rater contrast effect on the co-twins (who were both male and female) of male probands than of female probands. In twin analyses of the A-TAC and Conners ADHD scale, rater contrast effects have been modeled and shown to be modest^{9,33}, suggesting that rater contrast effects are unlikely to be an adequate explanation for our findings.

In addition to the caveat of the small effect size, our study did have further limitations that need taking into account. Proband status was ascertained through use of dimensional questionnaire measures, as opposed to in-depth assessments of ADHD. The use of this approach would, however, have come at the cost of the large sample size. As alluded to above, only twins were used in this study. While we removed MZ twins to ensure that the genetic relatedness of the relatives in our sample was similar to fraternal siblings, it is important to know whether these findings extend to non-twin relatives in future. In defense of our use of a twin sample, on the other hand, there is evidence to indicate that ADHD traits are not elevated in twins relatives to singletons³⁴. Finally, we did not examine the dimensions of hyperactivity/impulsivity and inattentiveness separately. This was intentional; we already had conducted numerous statistical tests, necessitating adjustment of p-values for multiple comparisons. The inclusion of further comparisons would likely have yielded non-significant

results; nonetheless, future studies of the female protective effect against ADHD should examine the two core ADHD symptom domains separately.

Finally, our study did not take comorbidity into account. Females with ADHD are more likely to present with additional disorders, such as anxiety and depression, than males with ADHD³⁵. If one assumes a certain degree of common causal factors across ADHD and other neuropsychiatric disorders, as supported by recent twin studies³⁶⁻³⁷, then it is possible that females manifest with different symptoms at lower levels of exposure to etiological factors, with ADHD only emerging after greater exposure. This could be tested in the future using ADHD polygenic risk scores, for example.

To a certain degree, this study indicates that females are protected against behaviors characteristic of ADHD. While our findings do not speak to any specific mechanisms through which this effect may operate, this study indicates that further research on the female protective effect model is warranted in relation to ADHD, with a view to identify the specific biological basis of this effect. If the effect holds across multiple epidemiological methods, then it represents a plausible explanation for why fewer females than males develop ADHD, as well as assisting in the diagnostic process.

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.
2. Willcutt EG. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. *Neurotherapeutics*. 2012;9:490-499.
3. Nøvik TS, Hervas A, Ralston SJ et al. Influence of gender on attention-deficit/hyperactivity disorder in Europe—ADORE. *Eur Child Adolesc Psychiatry*. 2006;15(suppl 1):15-24.

4. Catalá-López F, Peiró S, Ridaó M, Sanfèlix-Gimeno G, Gènova-Maleras R, Catalá MA. Prevalence of attention deficit hyperactivity disorder among children and adolescents in Spain: a systematic review and meta-analysis of epidemiological studies. *BMC Psychiatry*. 2012;12:168.
5. Levy F, Hay DA, McStephen M, Wood C, Waldman I. Attention-deficit hyperactivity disorder: a category or a continuum? Genetic analysis of a large-scale twin study. *J Am Acad Child Adolesc Psychiatry*. 1997;36:737-744.
6. Sherman DK, Iacono WG, McGue MK. Attention-deficit hyperactivity disorder dimensions: a twin study of inattention and impulsivity-hyperactivity. *J Am Acad Child Adolesc Psychiatry*. 1997;36:745-753.
7. Polderman TJ, Derks EM, Hudziak JJ, Verhulst FC, Posthuma D, Boomsma DI. Across the continuum of attention skills: a twin study of the SWAN ADHD rating scale. *J Child Psychol Psychiatry*. 2007;48:1080-1087.
8. Greven CU, Rijdsdijk FV, Plomin R. A twin study of ADHD symptoms in early adolescence: hyperactivity-impulsivity and inattention show substantial genetic overlap but also genetic specificity. *J Abnorm Child Psychol*. 2011;39:265-275.
9. Larsson H, Anckarsäter H, Råstam M, Chang Z, Lichtenstein P. Childhood attention-deficit hyperactivity disorder as an extreme of a continuous trait: a quantitative genetic study of 8,500 twin pairs. *J Child Psychol Psychiatry*. 2012;53:73-80.
10. Skuse DH. Imprinting, the X-chromosome, and the male brain: explaining sex differences in the liability to autism. *Pediatr Res*. 2000;47:9-16.
11. Jacquemont S, Coe BP, Hersch M et al. A higher mutational burden in females supports a 'female protective model' in neurodevelopmental disorders. *Am J Hum Genet*. 2014;94:415-425.

12. Robinson EB, Lichtenstein P, Anckarsäter H, Happé F, Ronald A. Examining and interpreting the female protective effect against autistic behavior. *Proc Natl Acad Sci U.S.A.* 2013;110:5258-5262.
13. Eriksson JM, Lundström S, Lichtenstein P, Bejerot S, Eriksson E. Effect of co-twin gender on neurodevelopmental symptoms: a twin register study. *Mol Autism.* 2016;7:8.
14. Rhee SH, Waldman ID. Etiology of sex differences in the prevalence of ADHD: an examination of inattention and hyperactivity-impulsivity. *Am J Med Genet B Neuropsychiatr Genet.* 2004;127B:60-64.
15. Anckarsäter H, Lundström S, Kollberg L et al. The Child and Adolescent Twin Study in Sweden (CATSS). *Twin Res Hum Genet.* 2011;14:495-508.
16. Haworth CM, Davis OS, Plomin R. Twins Early Development Study (TEDS): a genetically sensitive investigation of cognitive and behavioral development from childhood to young adulthood. *Twin Res Hum Genet.* 2013;16:117-125.
17. Hansson SL, Svanström Röjvall A, Råstam M, Gillberg C, Gillberg C, Anckarsäter H. Psychiatric telephone interview with parents for screening of childhood autism-tics, attention-deficit hyperactivity disorder and other comorbidities (A-TAC): preliminary reliability and validity. *Br J Psychiatry.* 2005;187:262-267.
18. Larson T, Anckarsäter H, Gillberg C et al. The autism-tics, AD/HD and other comorbidities inventory (A-TAC): further validation of a telephone interview for epidemiological research. *BMC Psychiatry.* 2010;10:1.
19. Conners CK, Sitarenios G, Parker JD, Epstein JN. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *J Abnorm Child Psychol.* 1998;26:257-268.

20. Cohen, J. *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
21. R Core Team. *R: A language and environment for statistical computing*. Vienna: R Foundation for Statistical Computing; 2015.
22. Ebejer JL, Duffy DL, van der Werf J, et al. Genome-wide association study of inattention and hyperactivity-impulsivity measured as quantitative traits. *Twin Res Hum Genet*. 2013;16:560-574.
23. Zuk O, Schaffner SF, Samocha K, et al. Searching for missing heritability: designing rare variant association studies. *Proc Natl Acad Sci U.S.A.* 2014;111:455-436.
24. Baron-Cohen S, Scott FJ, Allison C et al. Prevalence of autism-spectrum conditions: UK school-based population study. *Br J Psychiatry*. 2009;194:500-509.
25. Werling DM, Geschwind DH. Recurrence rates provide evidence for sex-differential, familial genetic liability for autism spectrum disorders in multiplex families and twins. *Mol Autism*. 2015;6:27.
26. Martin J, Hamshere ML, Stergiakouli E, O'Donovan MC, Thapar A. Genetic risk for attention-deficit/hyperactivity disorder contributes to neurodevelopmental traits in the general population. *Biol Psychiatry*. 2014;76:664-671.
27. Wray NR, Lee SH, Mehta D, Vinkhuyzen AA, Dudbridge F, Middeldorp CM. Polygenic methods and their application to psychiatric traits. *J Child Psychol Psychiatry*. 2014;55:1068-1087.
28. Pettersson E, Sjölander A, Almqvist C, et al. Birth weight as an independent predictor of ADHD symptoms: a within-twin pair analysis. *J Child Psychol Psychiatry*. 2015;56:453-459.
29. Hultman CM, Torráng A, Tuvblad C, Cnattingius S, Larsson JO, Lichtenstein P. Birth weight and attention-deficit/hyperactivity symptoms in childhood and early

- adolescence: a prospective Swedish twin study. *J Am Acad Child Adolesc Psychiatry*. 2007;46:370-377.
30. Rucklidge JJ. Gender differences in ADHD: implications for psychosocial treatment. *Expert Rev Neurother*. 2008;8:643-55.
 31. Williamson D, Johnston C. Gender differences in adults with attention-deficit/hyperactivity disorder: A narrative review. *Clin Psychol Rev*. 2015;40:15-27.
 32. Neale MC, Maes HHM. *Methodology for Genetic Studies of Twins and Families*. Dordrecht, the Netherlands: Kluwer Academic Publishers; 2004.
 33. Ronald A, Simonoff E, Kuntsi J, Asherson P, Plomin R. Evidence for overlapping genetic influences on autistic and ADHD behaviours in a community twin sample. *J Child Psychol Psychiatry*. 2008;49:535-42.
 34. Moilanen I, Linna S, Ebeling H, et al. Are twins' behavioural/emotional problems different from singletons? *Eur Child Adolesc Psychiatry*. 1999;8(suppl 4):62-67.
 35. Dalsgaard S, Mortensen PB, Frydenberg M, Thomsen PH. Conduct problems, gender and adult psychiatric outcome of children with attention-deficit hyperactivity disorder. *Br J Psychiatry*. 2001;181:416-21.
 36. Pettersson E, Anckarsäter H, Gillberg C, Lichtenstein P. Different neurodevelopmental symptoms have a common genetic etiology. *J Child Psychol Psychiatry*. 2013;54:1356-65.
 37. Pettersson E, Larsson H, Lichtenstein P. Common psychiatric disorders share the same genetic origin: a multivariate sibling study of the Swedish population [Epub ahead of print]. *Mol Psychiatry*. 2015 Aug 25. Doi: 10.1038/mp.2015.116.

Table 1 Number of Probands

Measure	Sample	5%		10%	
		Male, n (%)	Female, n (%)	Male, n (%)	Female, n (%)
Total ADHD	CATSS	227 (70)	95 (30)	450 (69)	201 (31)
	TEDS	146 (70)	63 (30)	291 (68)	138 (32)
	Merged	373 (70)	158 (30)	741 (69)	339 (31)
Hyperactivity/Impulsivity	CATSS	208 (68)	100 (32)	382 (63)	229 (37)
	TEDS	142 (69)	65 (31)	242 (63)	140 (37)
	Merged	350 (68)	165 (32)	624 (63)	369 (37)
Inattention	CATSS	238 (69)	109 (31)	468 (66)	237 (34)
	TEDS	141 (71)	57 (29)	255 (69)	116 (31)
	Merged	379 (70)	166 (30)	723 (67)	353 (33)

Note: ADHD = attention-deficit/hyperactivity disorder; CATSS = Child and Adolescent Twin Study in Sweden; TEDS = Twins Early Development Study.

Table 2 Descriptive Statistics

Measure	Cronbach's α	Possible Range of Scores	\bar{x} Full Sample (SD)	\bar{x} Males (SD)	\bar{x} Females (SD)	Skew
A-TAC ^a	.92	0-19	2.10 (3.21)	2.54 (3.54)	1.62 (2.73)	2.34
Conners ADHD ^b	.91	0-54	10.84 (9.00)	12.67 (9.71)	9.04 (7.85)	1.37
A-TAC Hyp/Imp ^c	.89	0-10	0.99 (1.69)	1.17 (1.85)	0.81 (1.48)	2.53
A-TAC Inatten. ^d	.90	0-9	1.03 (1.73)	1.28 (1.91)	0.78 (1.49)	2.23
Conners Hyp/Imp ^e	.89	0-27	5.57 (4.93)	6.39 (5.28)	4.78 (4.41)	1.33
Conners Inatten. ^f	.91	0-27	5.27 (5.04)	6.29 (5.45)	4.26 (4.37)	1.41

Note: ADHD = attention-deficit/hyperactivity disorder; A-TAC = Autism-tics and other comorbidities inventory; Conners ADHD = ADHD subscale of the Conners' Parent Rating Scale; hyp = hyperactivity; imp = impulsivity; inatten = inattention.

^a Mean A-TAC scores were significantly higher for males than females in the full sample, $t_{6539.22}=11.90$, $p<.001$, $d=.29$

^b Mean Conners ADHD scores were significantly higher for males than females in the full sample, $t_{3843.64}=13.08$, $p<.001$, $d=.42$

^c Mean A-TAC Hyperactivity/Impulsivity scores were significantly higher for males than females in the full sample, $t_{6431.70}=8.95$, $p<.001$, $d=.22$

^d Mean A-TAC Inattention scores were significantly higher for males than females in the full sample, $t_{6369.05}=12.08$, $p<.001$, $d=.30$

^e Mean Conners ADHD Hyperactivity/Impulsivity scores were significantly higher for males than females in the full sample, $t_{3890.60}=10.50$, $d=.34$

Table 3 Analysis of Continuous Traits of Attention-Deficit/Hyperactivity Disorder (ADHD) in Co-Twins

5%			
	CATSS	TEDS	Merged Samples
Co-Twin of Male Proband \bar{x}	0.43 (1.18)	0.62 (0.89)	0.51 (1.08)
Co-Twin of Female Proband \bar{x}	0.69 (1.23)	0.79 (1.02)	0.73 (1.15)
Co-Twin of Control \bar{x}	-0.03 (0.98)	-0.04 (0.99)	-0.03 (0.99)
Omnibus ANOVA	$F_{2,6688}=46.39, p<.01$	$F_{2,4040}=51.63, p<.001$	$F_{2,10731}=95.90, p<.001$
Planned Contrast	$t_{6688}=-2.10, p=.16, d=.05$	$t_{4040}=-1.10, p=.27, d=.03$	$t_{10731}=-2.38, p<.05, d=.05$
10%			
	CATSS	TEDS	Merged Samples
Co-Twin of Male Proband \bar{x}	0.38 (1.11)	0.55 (0.89)	0.45 (1.04)
Co-Twin of Female Proband \bar{x}	0.62 (1.14)	0.79 (0.87)	0.69 (0.79)
Co-Twin of Control \bar{x}	-0.05 (0.97)	-0.07 (0.99)	-0.06 (0.98)
Omnibus ANOVA	$F_{2,6688}=79.35, p<.01$	$F_{2,4040}=102.30, p<.001$	$F_{2,10731}=175.90, p<.001$
Planned Contrast	$t_{6688}=-2.84, p<.01, d=.07$	$t_{4040}=-2.36, p=.08, d=.07$	$t_{10731}=-3.73, p<.001, d=.07$

Note: Merged Samples are analyses of both Child and Adolescent Twin Study in Sweden (CATSS) and Twins Early Development Study (TEDS), merged into a single dataset. Omnibus analysis of variance (ANOVA) is a comparison of all three conditions (co-twins of male probands, co-twins of female probands, and co-twins of controls); planned contrast is a comparison of co-twins of male probands and co-twins of female probands.

Table 4 Analyses of Categorical Recurrence Rates

CATSS					
5%			10%		
	Co-Twin “Affected”	Co-Twin “Unaffected”		Co-Twin “Affected”	Co-Twin “Unaffected”
Male Proband	28 (12%)	199 (88%)	Male Proband	40 (9%)	410 (91%)
Female Proband	20 (21%)	75 (79%)	Female Proband	30 (15%)	171 (85%)
$\chi^2_1=3.35, p=.14, OR=0.53 (0.28/0.99)$			$\chi^2_1=4.67, p=.06, OR=0.57 (0.34/0.92)$		
TEDS					
5%			10%		
	Co-Twin “Affected”	Co-Twin “Unaffected”		Co-Twin “Affected”	Co-Twin “Unaffected”
Male Proband	32 (22%)	114 (78%)	Male Proband	83 (29%)	208 (71%)
Female Proband	21 (33%)	42 (67%)	Female Proband	52 (38%)	86 (62%)
$\chi^2_1=2.46, p=.24, OR=0.56 (0.29/1.08)$			$\chi^2_1=3.23, p=.14, OR=0.66 (0.43/1.01)$		
Merged Samples					
5%			10%		
	Co-Twin “Affected”	Co-Twin “Unaffected”		Co-Twin “Affected”	Co-Twin “Unaffected”
Male Proband	60 (16%)	313 (84%)	Male Proband	163 (22%)	578 (78%)
Female Proband	41 (26%)	117 (74%)	Female Proband	97 (29%)	242 (71%)
$\chi^2_1=6.38, p<.05, OR=0.54 (0.35/0.86)$			$\chi^2_1=5.21, p<.05, OR=0.70 (0.52/0.94)$		

Note: 5% and 10% indicate which cut-off was used to select probands in each analysis (highest scoring 10% of each sample or highest scoring 5% of each sample). Merged samples are analyses of both Child and Adolescent Twin Study in Sweden (CATSS) and Twins Early Development Study (TEDS) merged into a single dataset.

Figure 1: Mean co-twin scores for a) full-scale attention-deficit/hyperactivity disorder (ADHD), b) hyperactivity/impulsivity, and c) inattention for the highest scoring 10% in all analyses. Note: CATSS = Child and Adolescent Twin Study in Sweden; TEDS = Twins Early Development Study.

Supplementary Materials*Table S1 Analyses of Hyperactivity/Impulsivity Continuous Scores*

Continuous Scores (5%)			
	CATSS	TEDS	Merged Samples
Co-twin of male proband \bar{x}	0.36 (1.19)	0.74 (0.85)	0.51 (1.08)
Co-twin of female proband \bar{x}	0.72 (1.23)	0.99 (0.85)	0.83 (1.10)
Co-twin of control \bar{x}	-0.02 (0.98)	-0.04 (0.99)	-0.03 (0.98)
Omnibus ANOVA	$F_{2,6696}=41.65, p<.001$	$F_{2,4038}=77.06, p<.001$	$F_{2,10737}=109.60, p<.001$
Planned contrast	$t_{6696}=-3.04, p<.01, d=.04$	$t_{4038}=-1.76, p=.08, d=.05$	$t_{10737}=-10.06, p<.001, d=.19$
Continuous Scores (10%)			
	CATSS	TEDS	Merged Samples
Co-twin of male proband \bar{x}	0.36 (1.18)	0.69 (0.84)	0.49 (1.07)
Co-twin of female proband \bar{x}	0.52 (1.18)	0.81 (0.90)	0.63 (1.09)
Co-twin of control \bar{x}	-0.04 (0.97)	-0.08 (0.98)	-0.06 (0.97)
Omnibus ANOVA	$F_{2,6696}=62.08, p<.001$	$F_{2,4038}=121.20, p<.001$	$F_{2,10737}=167.30, p<.001$
Planned contrast	$t_{6696}=-7.66, p<.001, d=.09$	$t_{4038}=-11.85, p<.001, d=.37$	$t_{10737}=-13.31, p<.001, d=.26$

Note: ANOVA = analysis of variance; CATSS = Child and Adolescent Twin Study in Sweden; TEDS = Twins Early Development Study.

Table S2 Analyses of Hyperactivity/Impulsivity Categorical Recurrence Rates

CATSS					
5%			10%		
	“Affected” Co-Twin	“Unaffected” Co-Twin		“Affected” Co-Twin	“Unaffected” Co-Twin
Male Proband	23 (11%)	185 (89%)	Male Proband	41 (11%)	341 (89%)
Female Proband	18 (18%)	82 (82%)	Female Proband	30 (13%)	199 (87%)
$\chi^2_1=2.25, p=.13, OR=0.57 (0.29-1.11)$			$\chi^2_1=0.57, p=.45, OR=0.80 (0.48-1.31)$		
TEDS					
5%			10%		
	“Affected” Co-Twin	“Unaffected” Co-Twin		“Affected” Co-Twin	“Unaffected” Co-Twin
Male Proband	30 (21%)	112 (79%)	Male Proband	62 (25%)	180 (75%)
Female Proband	19 (29%)	46 (71%)	Female Proband	50 (36%)	90 (64%)
$\chi^2_1=1.20, p=.27, OR=0.64 (0.33-1.27)$			$\chi^2_1=3.89, p=.05, OR=0.62 (0.40-0.97)$		
Merged Samples					
5%			10%		
	“Affected” Co-Twin	“Unaffected” Co-Twin		“Affected” Co-Twin	“Unaffected” Co-Twin
Male Proband	53 (15%)	297 (85%)	Male Proband	131 (21%)	493 (79%)
Female Proband	37 (22%)	128 (78%)	Female Proband	101 (27%)	268 (73%)
$\chi^2_1=3.63, p=.06, OR=0.68 (0.39-0.99)$			$\chi^2_1=4.92, p<.05, OR=0.71 (0.52-0.95)$		

Note: CATSS = Child and Adolescent Twin Study in Sweden; OR = odds ratio; TEDS = Twins Early Development Study.

Table S3 Analyses of Inattention Continuous Scores

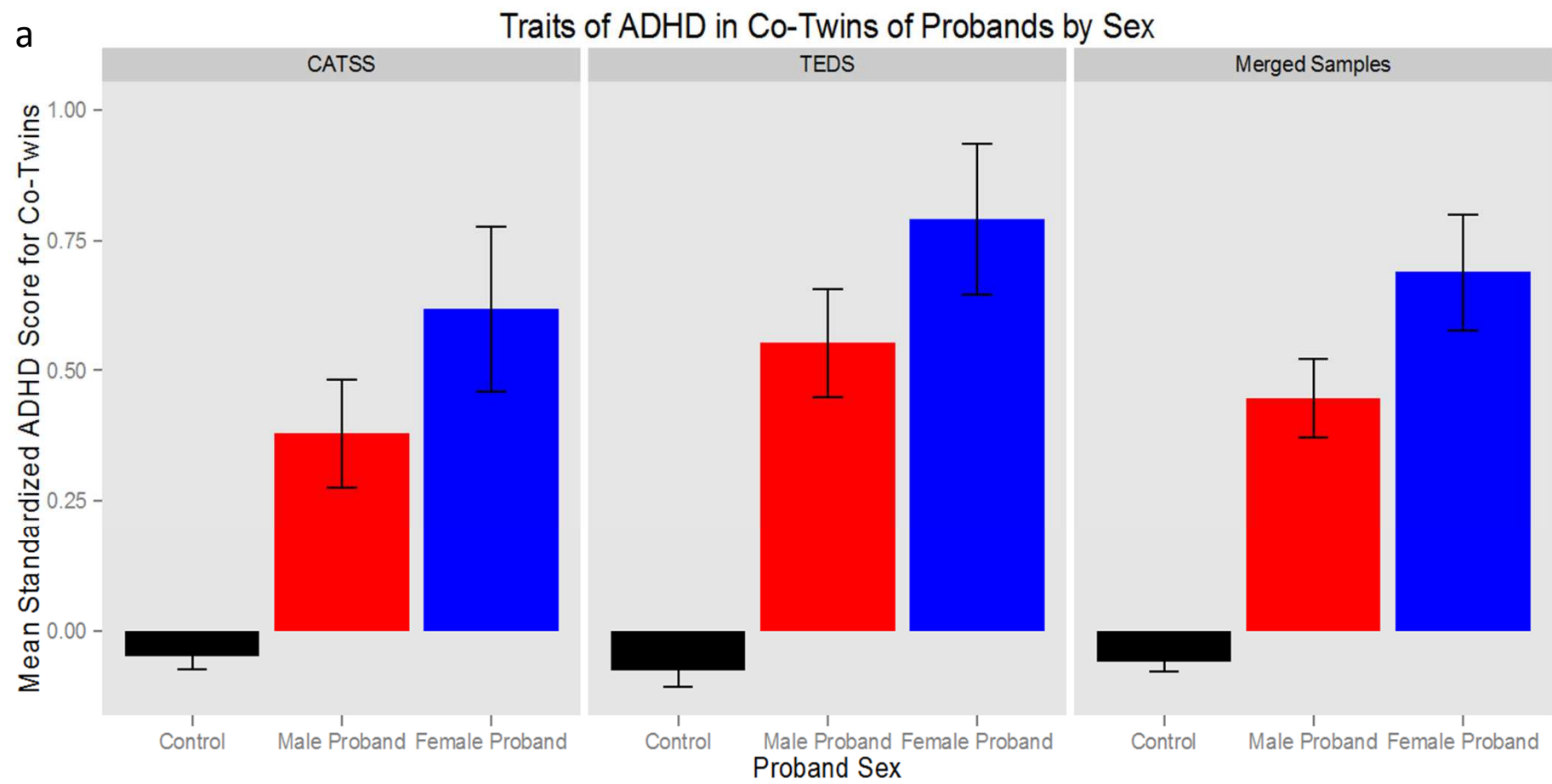
5%			
	CATSS	TEDS	Merged Samples
Co-twin of male proband \bar{x}	0.30 (1.09)	0.31 (1.01)	0.30 (1.06)
Co-twin of female proband \bar{x}	0.57 (1.28)	0.44 (1.15)	0.53 (1.24)
Co-twin of control \bar{x}	-0.02 (0.99)	-0.02 (0.99)	-0.02 (0.99)
Omnibus ANOVA	$F_{2,6691}=29.71, p<.001$	$F_{2,4038}=13.17, p<.001$	$F_{2,10732}=42.56, p<.001$
Planned contrast	$t_{6691}=-2.37, p<.05, d=.03$	$t_{4038}=-0.84, p=.40, d=.03$	$t_{10732}=-6.18, p<.001, d=.12$
10%			
	CATSS	TEDS	Merged Samples
Co-twin of male proband \bar{x}	0.26 (1.09)	0.39 (0.97)	0.31 (1.05)
Co-twin of female proband \bar{x}	0.46 (1.20)	0.51 (1.00)	0.48 (1.13)
Co-twin of control \bar{x}	-0.04 (0.98)	-0.04 (0.99)	-0.04 (0.98)
Omnibus ANOVA	$F_{2,6691}=46.07, p<.001$	$F_{2,4038}=38.50, p<.001$	$F_{2,10732}=83.02, p<.001$
Planned contrast	$t_{6691}=-6.28, p<.001, d=.15$	$t_{4038}=-6.75, p<.001, d=.21$	$t_{10732}=-9.06, p<.001, d=.17$

Note: ANOVA = analysis of variance; CATSS = Child and Adolescent Twin Study in Sweden; TEDS = Twins Early Development Study.

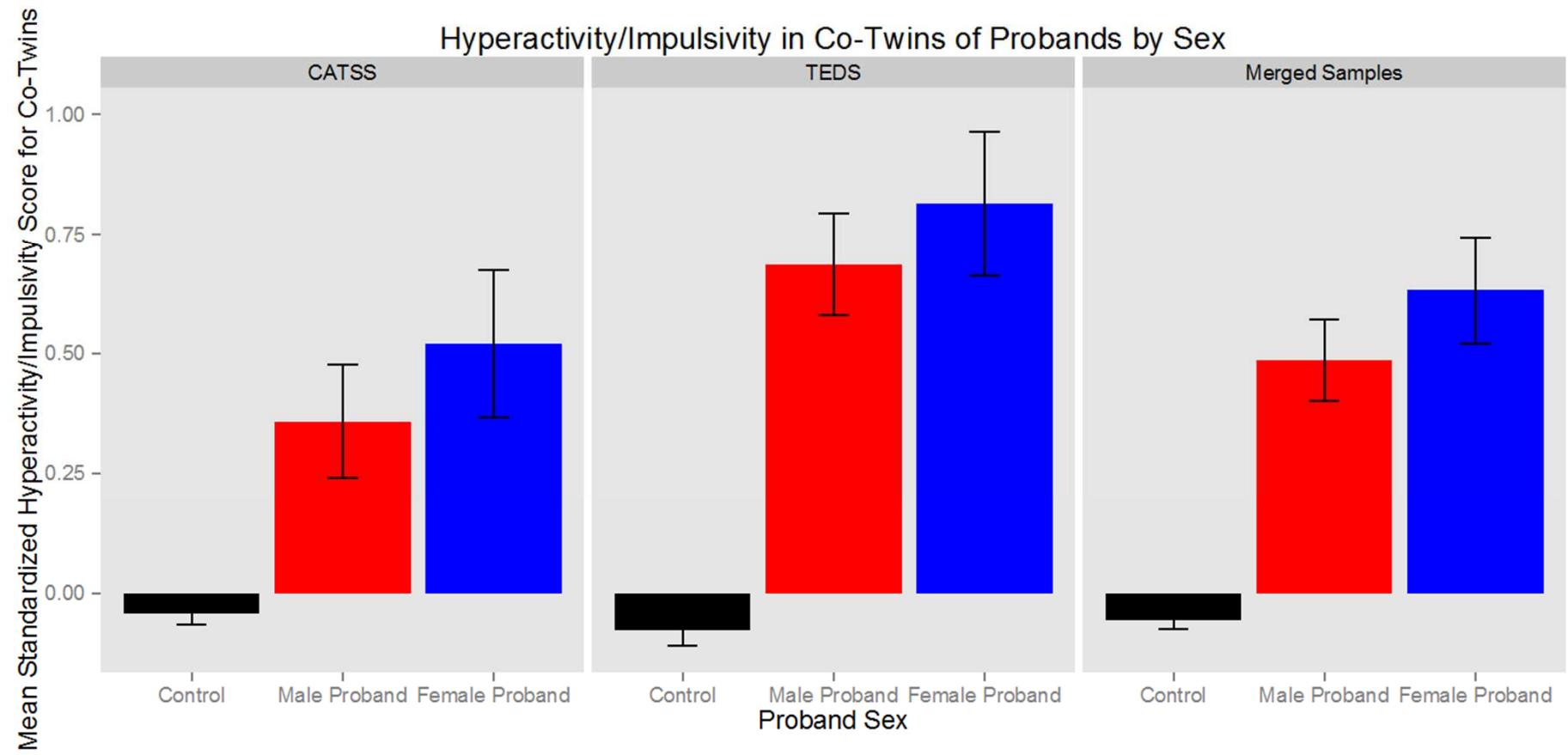
Table S4 Analyses of Inattention Categorical Recurrence Rates

CATSS					
5%			10%		
	“Affected” Co-Twin	“Unaffected” Co-Twin		“Affected” Co-Twin	“Unaffected” Co-Twin
Male Proband	22 (9%)	216 (91%)	Male Proband	80 (17%)	388 (83%)
Female Proband	22 (20%)	87 (80%)	Female Proband	56 (26%)	181 (74%)
$\chi^2_1=7.12, p<.05, OR=0.40 (0.21-0.76)$			$\chi^2_1=3.91, p=.05, OR=0.67 (0.45-0.98)$		
TEDS					
5%			10%		
	“Affected” Co-Twin	“Unaffected” Co-Twin		“Affected” Co-Twin	“Unaffected” Co-Twin
Male Proband	14 (10%)	127 (90%)	Male Proband	45 (18%)	210 (82%)
Female Proband	13 (23%)	44 (77%)	Female Proband	30 (26%)	86 (74%)
$\chi^2_1=4.67, p<.05, OR=0.37 (0.16-0.85)$			$\chi^2_1=2.85, p=.09, OR=0.61 (0.36-1.04)$		
Merged Samples					
5%			10%		
	“Affected” Co-Twin	“Unaffected” Co-Twin		“Affected” Co-Twin	“Unaffected” Co-Twin
Male Proband	36 (9%)	343 (91%)	Male Proband	125 (17%)	598 (83%)
Female Proband	35 (21%)	131 (79%)	Female Proband	86 (32%)	267 (68%)
$\chi^2_1=12.67, p<.001, OR=0.39 (0.24-0.65)$			$\chi^2_1=7.09, p<.05, OR=0.65 (0.48-0.89)$		

Note: CATSS = Child and Adolescent Twin Study in Sweden; OR = odds ratio; TEDS = Twins Early Development Study.



b



C

